Remarks

Upon entry of the above amendment, claims 1-14 will be pending in the present application. Applicants have amended clams 9 and 11 to make them independent. Applicants have amended the claims to correct syntax and put them in better condition for allowance. Applicants have not raised any issue of new matter.

Issue Under 35 U.S.C. §112

Claim 14 stands rejected under 35 U.S.C. §112, first paragraph as only being enabling for treatment and not prevention. Applicants have amended claims 14 to expedite prosecution.

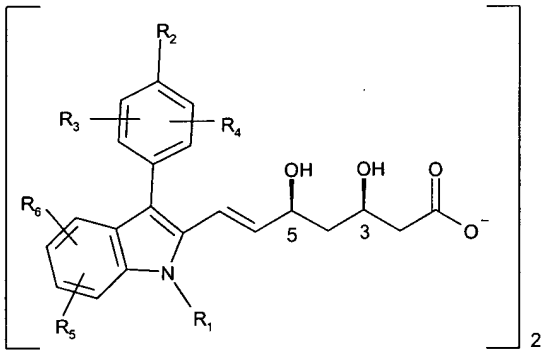
Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kathawala '772 (USP 5,354,772) and Ekwuribe '692 (USP 6,479,692). Applicants respectfully disagree that cited prior art establishes a prima facie case of obviousness.

Distinctions Between the Present Invention and Kathawala '772 and Ekwuribe '692

As stated in the previous response, the present invention provides calcium salts of indole derived statins of the formula



(IA)

More specifically in claim 7, Applicants claim a crystalline calcium salt of formula IA wherein R_1 is isopropyl, R_2 is fluorine and R_3, R_4, R_5 and R_6 are hydrogen, designated herein as Fluvastatin calcium, in a highly crystalline form. In claim 8, Applicants claims the crystalline calcium salt with a specific X-ray powder diffraction. In addition, Applicants claim methods for

the preparing of the crystalline calcium salt of Fluvastatin, pharmaceutical compositions comprising the crystalline calcium salt of fluvastatin and a method of treating comprising administering the crystalline calcium salt of fluvastatin..

Kathawala '772 discloses indole analogs of mevalonolactone and derivatives thereof. The Examiner notes that the Kathawala '772 discloses the potassium and sodium salts of the compounds, especially fluvastatin. In Table III of Kathawala ''772 only discloses the potassium salt and sodium salt.

The Examiner admits that Kathawala '772 fails to disclose the calcium salt, but provides Ekwuribe '692 to disclose the obviousness between pharmaceutically acceptable salts. The list provided by Ekwuribe '692 is a generic definition of possible pharmaceutically acceptable salts but the list provides no actual direction or suggestion that a particular salt would work with different compounds.

Kathawala '772 in view of Ekwuribe '692 may invite one to experiment by stating that calcium salts are known to be pharmaceutically acceptable salts; however, a skilled artisan would not have had a reasonable expectation of success for a crystalline, more stable salt form of fluvastatin.

As stated in the specification on page 1, last paragraph, a skilled artisan in the formulation art knows that higher crystallinity and lower hygroscopicity leads to improved chemical stability and longer shelf life. Applicants by making the calcium salt of fluvastatin discovered a more crystalline form of fluvastatin with improved chemical stability. The cited prior art failed to suggest a method of preparation that would provide the crystalline salt formation with the specific X-ray crystal powder diffraction.

Applicants respectfully assert that the specification on its own provides support for the argument that the instant invention has unexpected results over the cited prior art. However, Applicants can provide the following data in the form of a Declaration, if needed.

As mentioned above and in the specification on page 1, hygroscopicity of Fluvastatin sodium impose particular requirements on the manufacture and storage of pharmaceutical compositions comprising Fluvastatin sodium. Consequently, new forms of Fluvastatin having improved chemical stability are desired. Discovery of such a stable fluvastatin would make the preparation of pharmaceutical formulations of Fluvastatin with less need for stabilizing agents and with prolonged shelf life, and with the possibility of being provided in less sophisticated packages (page 1 of the specification).

Applicants have resolved this problem by providing a new salt (calcium salt) with lower hygroscopicity and the capacity to form crystals.

The data below supports an unexpected results assertion for the claimed Fluvastatin calcium salt:

Experimental protocol for measurement:

About 13 mg of powder was dried at 0% RH (Relative Humidity) and measured at RH values of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 95% on a humidity microbalance (DVS from Surface Measurement Systems). The sample temperature throughout the experiment was approximately 23°C and the criterion for RH change was dm/dt of < 0.002%.

dm/dt: change in weight of a sample over time at a given relative humidity

Results:

The calcium salt is less hygroscopic (2.8% gain at 84%RH) than the sodium salt (26% gain/84%RH).

Applicants respectfully assert that the specification fully supports the assertion of unexpected results; however, if needed, the results above show a clear and a significant advantage of the calcium salt over the sodium salt. The discovery that the calcium salt has greatly improved the crystallinity, which then leads to chemical stability and longer shelf life, is clearly a non-obvious step.

Applicants respectfully submit that the combined references fail to disclose or suggest the calcium salts claimed in the present invention. The cited references fail to show an actual equivalence between sodium salts and calcium salts. More importantly, the Ekwuribe '692 reference is mainly an invitation to experiment, which is not the legal standard of obviousness. Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Conclusion

Applicants have addressed all outstanding issues present in the Office Action. Applicants respectfully submit the present invention is patentable as claimed.

Respectfully submitted,

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